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Sodium-glucose co-transporter 2 (SGLT2) inhibitors=a brief review

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ABSTRACT

Sodium-glucose co-transporter-2 inhibitors are novel antihyperglycemic agents which have crucial effects on the heart and kidneys beyond their glucose-lowering features. Their main clinical benefits have been reported in individuals with type 2 diabetes mellitus, chronic kidney disease, heart failure, and proteinuria. However, adverse reactions (euglycemic ketoacidosis, kidney dysfunction, genital and urinary tract infections, hypovolemia, etc) remain to be the main object of the debate regarding their use. The recruited data have encouraged clinicians to use those medicines in individuals who fit the indications for use.

Keywords: Sodium-glucose co-transporter, diabetes mellitus, heart failure, kidney disease

INTRODUCTION

Sodium-glucose co-transporter-2 (SGLT-2) inhibitors, also called gliflozines or flozines, are blood glucose-lowering agents that act on SGLT-2 proteins expressed on the surface of various organ cells, especially in the proximal renal tubules. Dapagliflozin, canagliflozin, empagliflozin, and ertugliflozin are FDA-approved SGLT-2 inhibitors for the treatment of adult patients with type 2 diabetes mellitus (DM) to improve glycemic control in addition to diet and exercise.[1]

In March 2013, canagliflozin was approved by the FDA as the first SGLT-2 inhibitor in type 2 DM treatment that does not induce hypoglycemia and promotes weight loss by losing 300 to 400 kcal/day.[2] It also reduces the risk of cardiovascular (CV) adverse events in patients with type 2 DM with underlying CV disease and reduces the risk of developing end-stage renal disease (ESRD), CV mortality and hospitalization for heart failure in patients with type 2 DM with diabetic nephropathy and albuminuria.[3]

Dapagliflozin was the second SGLT2 inhibitor that received FDA approval in 2014. It is indicated in adult patients with type 2 DM to lower high blood glucose in adjunct to diet and exercise. Additionally, it demonstrates beneficial features; minimizing the hospitalization attributed to heart failure in type 2 DM patients with underlying CV disease or various CV risk factors, reducing the risk of CV mortality and hospitalization in adult patients with heart failure with decreased ejection fraction with New York Heart Association (NYHA) classification II-IV.[4,5] It has also an indication of use to reduce the risk of decline of estimated glomerular filtration rate (eGFR), ESRD, CV mortality, and hospitalization due to heart failure in chronic kidney disease (CKD) patients.[4,5]

In August 2014, empagliflozin became the third SGLT inhibitor to receive approval from the FDA.[6] It achieved similar use of indications with dapagliflozin. Recent evidence has extended the indications of the use of SGLT2 inhibitors to patients with HF, with and without T2D, finding that SGLT-2 inhibitors (particularly dapagliflozin and empagliflozin) are effective therapeutic agents for the treatment and prevention of HF.[7] Finally, in 2017, ertugliflozin received approval from the FDA in order to use for adult patients with type 2 DM to improve higher blood glucose in addition to diet and exercise.[8]

Distribution of SGLT2 Proteins and Their Effects

Sodium-dependent glucose cotransporters (or sodium-glucose-linked transporters, SGLT) are a family of glucose transporters encoded by the SLC5A1 gene family and found in the intestinal mucosa (enterocytes) of the small intestine (SGLT1) and in the proximal tubule of the nephron (SGLT2). To date, 10 additional members of the human SLC5A protein family have been described.[9,10] The distribution of all types of SGLT2 proteins in the body is given in **Table 1**.[11-13]

Table 1. SGLT2 transmembrane proteins are being expressed widely in the body

Protein	Co-transporting	Tissue/Organ
SGLT1	Glucose/Galactose	Intestine, trachea, kidney, heart, brain, testis, prostate
SGLT2	Glucose	Kidney, brain, liver, thyroid, muscle, heart
SGLT3	Glucose	Intestine, testis, uterus, lung, brain, thyroid
SGLT4	Glucose, Mannose	Intestine, kidney, liver, brain, lung, trachea, uterus, pancreas
SGLT5	Glucose, Galactose	Kidney
SGLT6	D-chiro inositol	brain, kidney, intestine

Adopted from the references 13. SGLT; sodium-glucose co-transporter-2

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The Na^+/K^+-ATPase on the basolateral membrane of proximal tubule cells induces ATP molecules to move three sodium ions out of the cell and two potassium ions into the cell. This movement creates a downward sodium ion gradient from the outside to the inside of the proximal tubule cell.

The SGLT transmembrane proteins use the energy of this downward sodium ion gradient established by the ATPase pump to transport glucose across the apical membrane against an upward glucose gradient. These co-transporters are also referred to as secondary active transport. Members of the GLUT family of glucose uniporters then transport glucose across the basolateral membrane into the peritubular capillaries. Because sodium and glucose move across the membrane in the same direction, SGLT1 and SGLT2 are called symporters. GLT2, located in the S1 segment, is a low-affinity, high-capacity transporter that reabsorbs up to 90% of filtered glucose (**Table 2**).[13] SGLT1, located in the S3 segment, is a high-affinity, low-capacity transporter that reabsorbs the remaining 10%.[14,15] Of course, sodium can be consumed, so the sodium-hydrogen antiporter first brings sodium into the cell. Therefore, glucose is actually moved by pushing protons out of the cell, with sodium as an intermediary. SGLT-2 inhibitors suppress renal glucose reabsorption and thereby increase urinary glucose excretion by lowering the renal threshold for glucose excretion.[14] Hyperglycemia is thereby ameliorated. However, SGLT-2 inhibitors inhibit the reabsorption of only ~30-50% of the glucose filtered into the proximal tubules. The answer to why they are unable to inhibit 90% of glucose reabsorption in humans is unclear.[16,17]

Table 2. The comparison of SGLT1 and SGLT2

	SGLT1	SGLT2
Localization	Intestine, proximal convoluted tubule (segment 3)	proximal convoluted tubule (segment 1,2)
Capacity	Low	High
Affinity	High	Low
Contribution to glucose reabsorption	10%	90%
Mutation/deficiency	Glucose and galactose malabsorption	familial renal glucosuria
Symptoms in case of illness	Diarrhea, glucosuria	glucosuria
Clinical course	Death if glucose and galactose are not restricted	benign
Inhibitors	Phlorizin	SGLT2 inhibitors

Adopted from the references 13, SGLT-2; Sodium-glucose co-transporter-2

Inhibition of SGLT-2-dependent glucose and sodium reabsorption leads to an increase in distal tubular sodium load. This not only inhibits the activity of the renin-angiotensin-aldosterone system, but also ameliorates failed tubuloglomerular feedback mechanisms, which include lowering intraglomerular renal pressure, promoting tubuloglomerular feedback, downregulating sympathetic activity, and reducing cardiac preload and afterload.[17,18]

Introduction of SGLT2 inhibitors and Management

SGLT2 inhibitors are effective at any stage of type 2 DM because of their unique, insulin-independent mechanism of action. Data support their use as add-on therapy to any other antidiabetic agent and as monotherapy in patients who cannot tolerate metformin. However, the degree of renal dysfunction and the possible development of side effects may limit its use. Patients of younger age, with an estimated glomerular filtration rate of at least 60 mL/min/1.73 m2 (renal function unimpaired), with established cardiovascular disease, without frequent genitourinary tract infections, overweight or obese, or with hypertension (moderate to high blood pressure) are likely to generally receive the greatest benefit from these drugs. Lower doses are recommended at the start of treatment with SGLT2 inhibitors. Consideration of concomitant therapies is also important to minimize the risk of adverse effects. The daily insulin dose should be reduced by 20% in patients with an HbA1c of less than 8.5% to avoid insulin withdrawal and minimize the risk of euglycemic diabetic ketoacidosis.[19,20] A brief overview of initiating treatment with SGLT2 inhibitors is provided in **Table 3**.

Table 3. Available forms of SGLT2 inhibitors and Their Dosages in Adults

Canagliflozin[21,22]

- 100 mg and 300 mg tablets for oral use.
- eGFR ≥60 ml/min/1.73 m2= 100-300 mg once daily
- eGFR ≥30 and < 60 ml/min/1.73 m2= 100 mg once daily
- eGFR <30 ml/min/1.73 m2= Initiating therapy with canagliflozin is not advised in patients with an eGFR of less than 30. Although 100 mg once daily may be administered in subjects with albuminuria >300 mg daily if already in use. This may further decrease ESRD risk, cardiovascular mortality, and hospitalization for heart failure and reduce the rise in serum creatinine in this subset of patients. Stopping medication 3 days before surgery may be safe. Before commencing check the volume status.

Dapagliflozin[4]

- 5 mg and 10 mg tablets for oral use
- eGFR ≥45 ml/min/1.73 m2= 5-10 mg once daily
- eGFR ≥25 and < 45 ml/min/1.73 m2= 5 mg once daily
- eGFR <30 ml/min/1.73 m2= Initiating medication in patients with eGFR less than 25 is not advised, but therapy may be continued to decrease the risk of declining eGFR, ESRD, cardiovascular mortality, and hospitalization for heart failure. Stopping medication 3 days before surgery may be safe. Before commencing check the volume status.

Empagliflozin[5]

- 10 mg and 25 mg tablets for oral use
- eGFR ≥45 ml/min/1.73 m2= 10-25 mg once daily
- eGFR <30 ml/min/1.73 m2= Initiating therapy with empagliflozin is not advised in patients with an eGFR of less than 30 ml/min/1.73 m2. However, therapy may be continued to decrease the risk of declining eGFR, ESRD, cardiovascular mortality, and hospitalization for heart failure. Empagliflozin is not advised in individuals with a diagnosis of type 1 DM as it increases the risk of diabetic ketoacidosis (DKA). Stopping medication 3 days before surgery may be safe. Before commencing check the volume status.

Ertugliflozin[23]

- 5 mg and 15 mg tablets for oral use
- eGFR ≥45 ml/min/1.73 m2= 5-15 mg once daily
- eGFR < ml/min/1.73 m2= Initiation of this medicinal product is not recommended in patients with an estimated glomerular filtration rate (eGFR) less than 45 mL/min/1.73 m2. It should be discontinued when eGFR is persistently less than 30 mL/min/1.73 m2 or CrCl is persistently less than 30 mL/min. It should not be used in patients with severe renal impairment, with end-stage renal disease (ESRD), or receiving dialysis, as there is no clinical data to support effectiveness in these patients. Ertugliflozin is not advised in individuals with a diagnosis of type 1 DM as it increases the risk of diabetic ketoacidosis (DKA). Stopping medication 3 days before surgery may be safe. Before commencing check the volume status.

eGFR; estimated glomerular filtration rate, ESRD; end-stage renal disease, DM; diabetes mellitus, DKA; diabetic ketoacidosis, CrCl; creatinine clearence

Adverse Reactions

Genital infections are probably the most common adverse effect of gliflozines. In clinical trials, fungal infections, urinary tract infections, and osmotic diuresis occurred more frequently in patients receiving gliflozines (**Table 4**). Because they can increase the absorption of ketone bodies from proximal tubule cells, they can specifically cause euglycemic DKA (DKA in which blood glucose is not elevated).[24] The perioperative period has been reported to be a particularly high risk for ketoacidosis. Therefore, consideration may be given to discontinuing SGLT2 inhibitors before surgery.[25]

Table 4. Common Adverse Reactions Reported in the Patients under SGLT-2 inhibitors[4,5,23,26]

Canagliflozin
• Genital mycotic infections in females (10.6% - 11.6%) • Urinary tract infections (4.4% - 5.9%) • Increased urination (4.6% - 5.1%) • Genital mycotic infections in males (3.8% - 4.2%) • Thirst (2.4% - 2.8%) • Constipation (1.8% - 2.4%) • Nausea (2.1% - 2.3%) • Vulvovaginal pruritus (1.6% - 3.2%)
Dapagliflozin[23]
• Genital mycotic infections in females (6.9% - 8.4%) • Nasopharyngitis (6.3% - 6.8%) • Urinary tract infections (4.3% - 5.7%) • Back pain (3.1% - 4.2%) • Nausea (2.5 - 2.8%) • Genital mycotic infections in males (2.7% - 2.8%) • Influenza (2.3% - 2.7%) • Dyslipidemia (2.1% - 2.5%) • Constipation (1.9% - 2.2%) • Discomfort during urination (1.6% - 2.1%) • Pain in extremities (1.7% - 2%)
Empagliflozin
• Urinary tract infection (7.6% - 9.3%) • Genital mycotic infections in females (5.4% - 6.4%) • Genital mycotic infections in males (1.6% - 3.1%) • Upper respiratory tract infection (3.1% - 4%) • Increased urination (3.2% - 3.4%) • Dyslipidemia (2.9% - 3.9%) • Arthralgia (2.3% - 2.4%) • Nausea (1.1% - 2.3%)
Ertugliflozin
• Genital mycotic infections in females (9.1% - 12.2%) • Urinary tract infection (4% - 4.1%) • Genital mycotic infections in males (3.7% - 4.2%) • Headache (2.9% - 3.5%) • Vaginal pruritus (2.4% - 2.8%) • Increased urination (2.4% - 2.7%) • Nasopharyngitis (2% - 2.5%) • Back pain (1.7% - 2.5%) • Decrease in weight (1.2% - 2.4%) • Thirst (1.4% - 2.7%)

Monitoring SGLT2 Inhibitor Users

Volume status is the most important consideration before initiation of SGLT-2 inhibitors because all patients can be hypovolemic at any age. Symptomatic hypotension and a transient increase in serum creatinine may be observed. Therefore, renal function and blood pressure should be routinely checked after initiation of SGLT-2 inhibitors. Individuals diagnosed with renal impairment receiving a loop diuretic and elderly patients on SGLT-2 inhibitor therapy should be monitored more closely because of a higher risk of complications related to volume depletion. A complete blood count, a metabolic panel including blood glucose, a lipid panel, and renal function tests should be routinely performed because changes in serum creatinine, eGFR, hematocrit, hemoglobin, low-density lipoprotein (LDL) cholesterol, serum bicarbonate, serum phosphate, and potassium may occur to varying degrees after initiation of treatment with an SGLT2 inhibitor.[27,28]

Treatment with SGLT2 inhibitors may cause necrotizing fasciitis of the perineum, also known as "Fournier's gangrene". If perineal necrotizing fasciitis is suspected, appropriate treatment with broad-spectrum antibiotics and, if necessary, surgical debridement should be initiated, and SGLT-2 inhibitors must be discontinued, other treatment options of therapeutic regimens for glycemic control should be used, and blood glucose levels should be monitored after the switch.[28,29]

Canagliflozin and ertugliflozin have been associated with lower limb amputations, so patients with peripheral vascular disease, history of amputation, neuropathy, high HbA1C at baseline, and diabetic foot ulcers should be closely monitored; infection or ulceration must be treated immediately. Lower extremity infections, gangrene, and foot ulcers are the common factor in the causes of amputations.[28]

CONCLUSION

SGLT2 inhibitors are promising new therapeutic options for the treatment of type 2 DM. Reabsorption of filtered glucose, mainly in the proximal renal tubules, is inhibited by their use. This results in glucose excretion in the urine and correction of diabetes-related hyperglycemia. In addition to their effect in ameliorating hyperglycemia, SGLT2 inhibitors offer potential benefits by lowering weight and blood pressure. One SGLT2 inhibitor, empagliflozin, has also been shown to have benefits on renal disease progression, cardiovascular and all-cause mortality, and hospitalization for heart failure. Adverse effects such as hypoglycemia and volume-dependent events necessitate re-monitoring after taking SGLT2 inhibitors. The elderly, patients receiving diuretics, previous orthostatic hypotension, blood pressure lability, or previous syncope are the main factors for the development of adverse reactions.

ETHICAL DECLARATIONS

Referee Evaluation Process: Externally peer-reviewed.

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